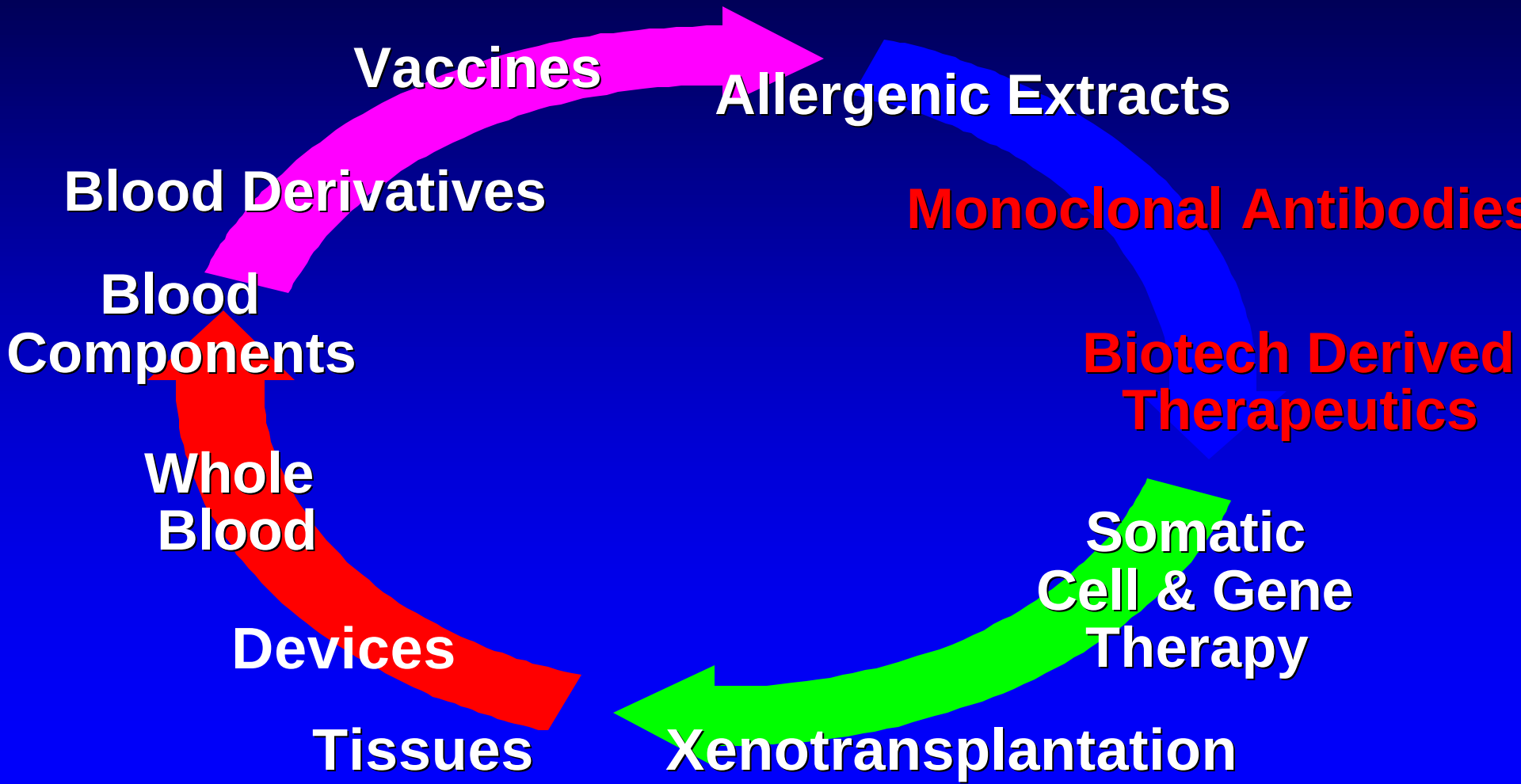

# Center for Biologics Evaluation and Research Update
# ISPE Annual Meeting

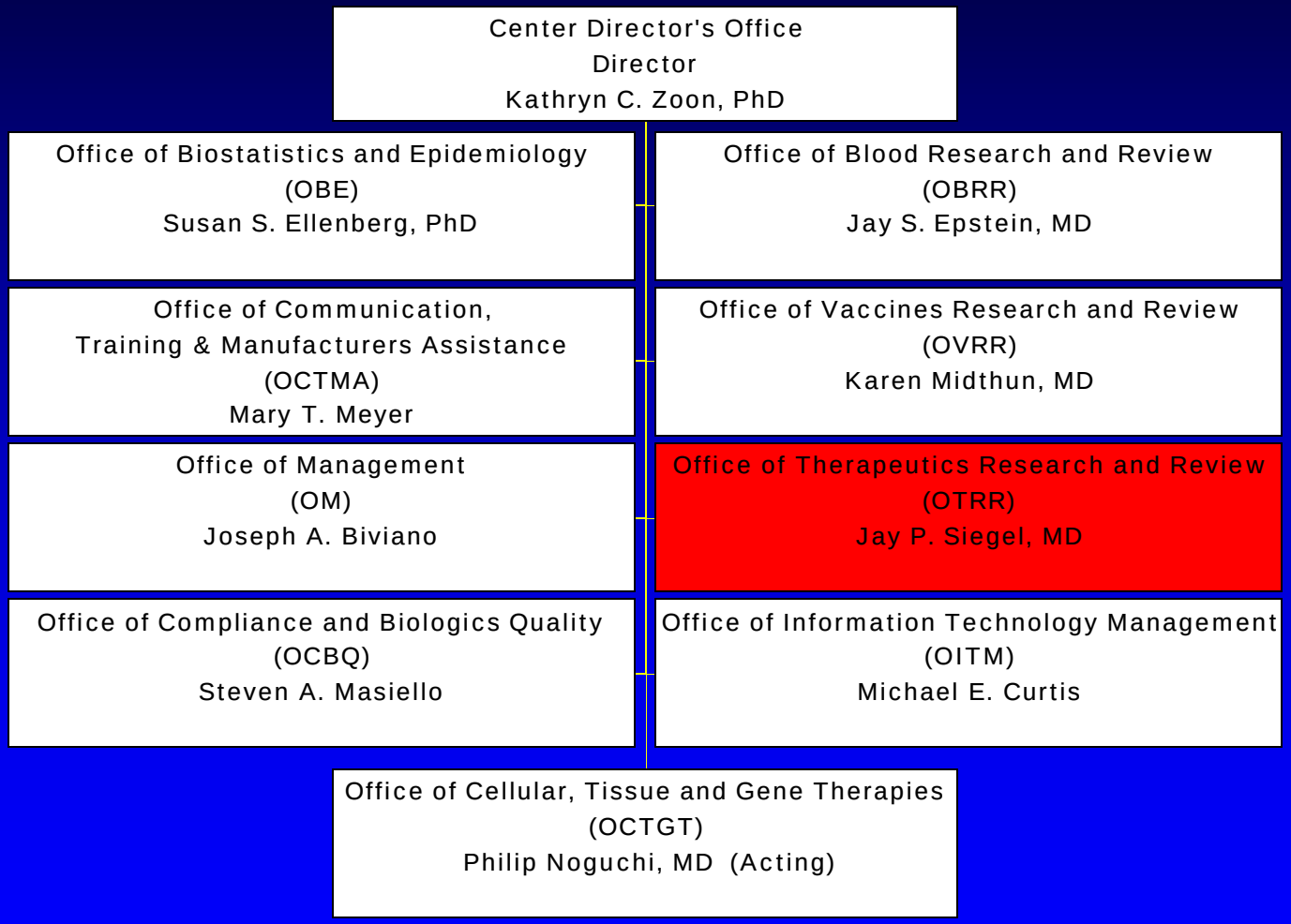
**Mark A. Elengold**

**November 4, 2002**

# BIOLOGICAL PRODUCTS REGULATED BY CBER



# CBER Organization



# What's Going

**Monoclonal antibodies**

**Cytokines, growth factors, enzymes, interferons -- (including recombinant versions)**

**Proteins intended for therapeutic use that are extracted from animals or microorganisms**

**Other therapeutic immunotherapies**

# What's Staying

- Monoclonal antibodies, cytokines, growth factors, or other proteins when used solely as an ex vivo constituent in a manufacturing process / when used solely as a reagent in the production of a product that is under the jurisdiction of CBER
- Viral-vectored gene insertions (i.e., "gene therapy")
- Products composed of human or animal cells or from physical parts of those cells

# What's Staying (continued)

- Plasma expanders
- Allergen patch tests
- Allergenics
- Antitoxins, antivenins, and venoms
- In vitro diagnostics
- Vaccines
- Toxoids and toxins intended for immunization

# CBER Priorities FY 2003

- **Ensure the safety and efficacy of biological products while facilitating their development and meeting Prescription Drug User Fee Act (PDUFA) goals**
- **Ensure the safety of, and public confidence in, the nation's blood supply and tissues**

# CBER Priorities FY 2003

- **Improve automated system to support the review and evaluation of biological products, e.g. EDR, e-CTD**
- **Implement New Office of Cellular, Tissue and Gene Therapy Products**
- **Develop effective measures for Counter Terrorism**
- **GMPs for the 21st Century**

# CBER Priorities FY 2003

- **Facilitate the development and approval of significant vaccine, blood and therapeutic products through review, policy formulation, regulation development, guidance issuance to industry, workshops and meetings**
- **Implement OC management initiatives**
- **Foster Interagency Collaborations,**

  **e.g. CBER/NCI CBER/NIAID**

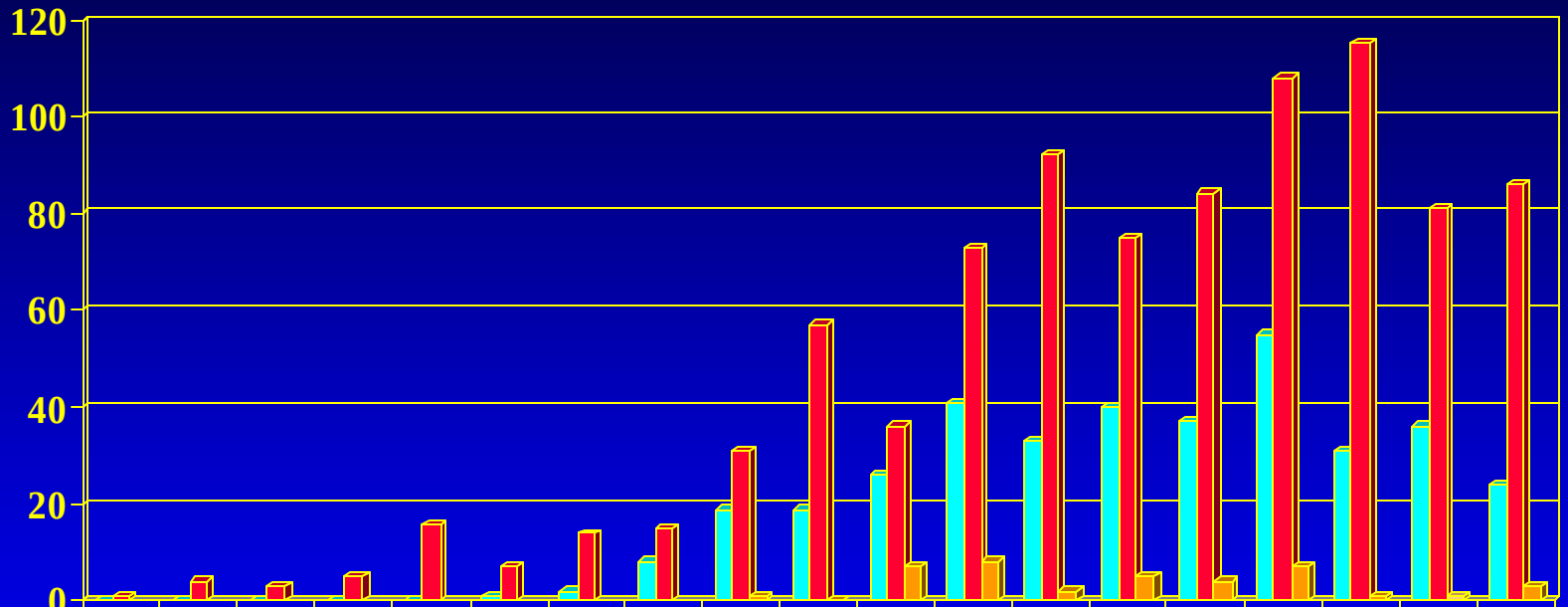
# Office of Cellular, Tissue, and Gene Therapies (OCTGT)

# Why?

- Increase in regulatory activities in the areas of cellular and tissue-based products, gene therapies, and all forms of stem cell transplantation.
- Consolidation of products into one office
  - Products getting more complex
  - New science advances
  - Need for seamless and transparent coordination and communication

# Gene Therapy, Somatic Cell Therapy, Xenotransplantation INDs/IDEs

## Received FY 1984 - FY 2002



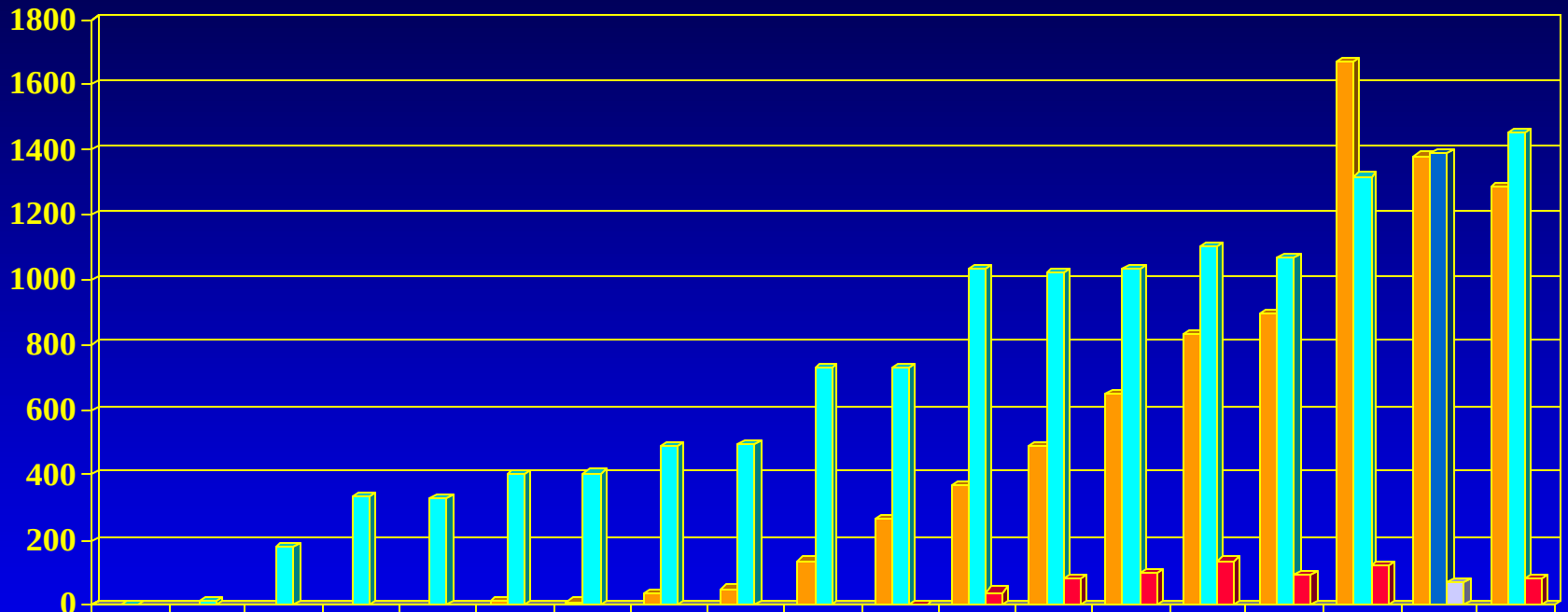

| | FY84 | FY85 | FY86 | FY87 | FY88 | FY89 | FY90 | FY91 | FY92 | FY93 | FY94 | FY95 | FY96 | FY97 | FY98 | FY99 | FY00 | FY01 | FY02 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GT INDs | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 8 | 19 | 19 | 26 | 41 | 33 | 40 | 37 | 55 | 31 | 36 | 24 |
| SCT INDs/IDEs | 1 | 4 | 3 | 5 | 16 | 7 | 14 | 15 | 31 | 57 | 36 | 73 | 92 | 75 | 84 | 108 | 115 | 81 | 86 |
| Xeno INDs | | | | | | | | | 1 | 0 | 7 | 8 | 2 | 5 | 4 | 7 | 1 | 1 | 3 |

Note: A total of 7 INDs were for Xeno and GT, and are included in the counts for both.

# Gene Therapy, Somatic Cell Therapy, Xenotransplantation

## IND/IDE Amendments

## Received FY 1984 - FY 2002




| | FY84 | FY85 | FY86 | FY87 | FY88 | FY89 | FY90 | FY91 | FY92 | FY93 | FY94 | FY95 | FY96 | FY97 | FY98 | FY99 | FY00 | FY01 | FY02 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GT Amend's | | | | | | 13 | 12 | 40 | 54 | 137 | 268 | 369 | 488 | 650 | 834 | 892 | 1670 | 1378 | 1285 |
| SCT Amend's | 1 | 14 | 180 | 337 | 328 | 403 | 405 | 488 | 494 | 730 | 728 | 1033 | 1023 | 1036 | 1105 | 1068 | 1315 | 1386 | 1453 |
| Xeno Amend's | | | | | | | | | | | 3 | 43 | 82 | 103 | 139 | 96 | 124 | 68 | 82 |

ote: A total of 317Amendments were for INDs that are both
eno and GT and are included in the counts for both..

r)RIMS:10/03/02

# Mission

- **Regulatory and review responsibilities:**
  - **Tissues**
  - **Cellular and Tissue-based products**
  - **Gene Therapies**
  - **Xenotransplantation**
  - **Unique assisted reproduction (ooplasm transfer)**
  - **Combination Products containing living cells/tissues**
- **Assure the safety, identity, purity and potency of novel products**

# Expertise

- Molecular and cell biology
- Viral and nonviral gene therapy vectors
- Nucleic acid chemistry
- Genomics
- Proteomics
- Tissue and Organ Regeneration
- Developmental and Reproductive Biology
- Stem Cell Biology and Physiology
- Medical
- Pharmacology/Toxicology

**Office of Cellular, Tissue, and Gene Therapies**

Dr. Philip Noguchi, (Acting) Office Director

Dr. Joyce Frey-Vasconcells, (Acting) Deputy Office Director

Regulatory Management Staff

(Acting) Chief, Ms. Andrea Wright

**Division of Cellular & Gene Therapies**
**Dr. Raj Puri, (Acting) Director**

**Division of Human Tissues**
**Dr. Ruth Solomon, (Acting) Division Director**

**Division of Clinical Evaluation & Pharmacology/Toxicology**
(Vacant)

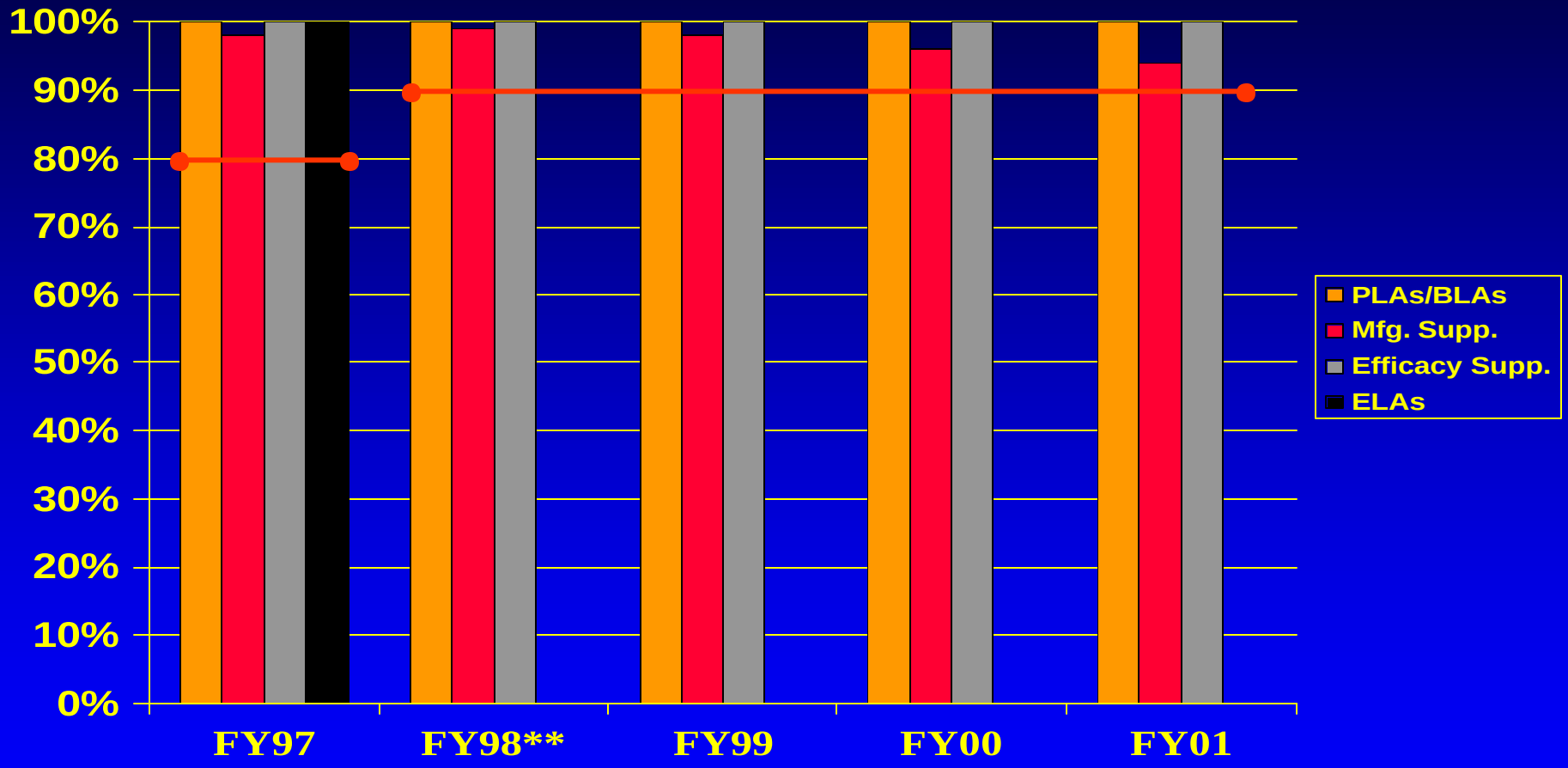
# The OTRR, CBER record

- Science-based regulation of biologic therapeutics at OTRR has played a central role in the development and availability of safe and effective products of biotechnology that are revolutionizing medicine.
- OTRR scientists/physicians work independently of but closely with regulated biotechnology.
  - Extraordinary number of meetings
  - Timely, science based guidance
- OTRR scientists/physicians have provided international leadership in the science-based regulation of biotechnology products.

# The OTRR, CBER record (continued)

- **The number of new product approvals is increasing.**
- **Despite the complexity and novelty of biotechnology products, review times and approval times compare favorably with those for other types of drugs.**
- **Biological therapeutics are often available first in the U.S.**
- **There has *never* been need to recall an OTRR-approved biotechnology drug due to safety concerns.**

# CBER User Fee Review Performance
# License Applications and Supplements
## % of First Actions Within Goal*
## By Cohort Fiscal Years 1997-2001




* PDUFA Performance Goals: FY97 - FY01=90% (Indicated by Red Lines)
** Beginning in FY98 ELAs were no longer included in PDUFA goals

Data through 30 Sep 02; FY 01 is not yet complete.

(253bp)RIMS 10/02/02

# CBER PDUFA II Procedural and Processing Goals Performance (as of October 31, 2002)

| Regulatory Meetings Management | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Actions Within Goal | | | Actions Overdue | | | | |
| Fiscal Year | Goal | Meeting Requests Received | Completed | Pending | Total | Completed | Pending | Total | % Completed Within Goal[1] | *PDUFA Goal* |
| FY 1999 | Response | 387 | 283 | 0 | 283 | 104 | 0 | 104 | 73% | *70%* |
| | Held | 364 | 321 | 0 | 321 | 43 | 0 | 43 | 88% | |
| | Minutes | 328 | 282 | 0 | 282 | 46 | 0 | 46 | 86% | |
| FY 2000 | Response | 312 | 302 | 0 | 302 | 10 | 0 | 10 | 97% | *80%* |
| | Held | 294 | 277 | 0 | 277 | 14 | 3 | 17 | 94% | |
| | Minutes | 251 | 229 | 0 | 229 | 19 | 3 | 22 | 91% | |
| FY 2001 | Response | 281 | 275 | 0 | 275 | 6 | 0 | 6 | 98% | *90%* |
| | Held | 246 | 218 | 21 | 239 | 6 | 1 | 7 | 97% | |
| | Minutes | 180 | 157 | 20 | 177 | 3 | 0 | 3 | 98% | |
| FY 2002 | Response | 412 | 399 | 0 | 399 | 12 | 1 | 13 | 97% | *90%* |
| | Held | 372 | 306 | 53 | 359 | 7 | 6 | 13 | 96% | |
| | Minutes | 288 | 245 | 27 | 272 | 5 | 11 | 16 | 94% | |

[1] - of those that have reached the goal date

# CBER PDUFA II Procedural and Processing Goals Performance – *cont.*
# (as of October 31, 2002)

**Special Protocol Assessment**

| Fiscal Year | Protocol Review Requests Received | Actions Within Goal | | | Actions Overdue | | | % Completed Within Goal[1] | *PDUFA Goal* |
|---|---|---|---|---|---|---|---|---|---|
| | | Completed | Pending | Total | Completed | Pending | Total | | |
| FY 1999 | 0 | | | | | | | | *60%* |
| FY 2000 | 0 | | | | | | | | *70%* |
| FY 2001 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 100% | *80%* |
| FY 2002 | 4 | 4 | 0 | 4 | 0 | 0 | 0 | 100% | *90%* |

**Major Dispute Resolution**

| Fiscal Year | Dispute Resolution Requests Received | Actions Within Goal | | | Actions Overdue | | | % Completed Within Goal[1] | *PDUFA Goal* |
|---|---|---|---|---|---|---|---|---|---|
| | | Completed | Pending | Total | Completed | Pending | Total | | |
| FY 1999 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 100% | *70%* |
| FY 2000 | 0 | | | | | | | | *80%* |
| FY 2001 | 2 | 2 | 0 | 2 | 0 | 0 | 0 | 100% | *90%* |
| FY 2002 | 4 | 4 | 0 | 4 | 0 | 0 | 0 | 100% | *90%* |

**Responses to Clinical Holds**

| Fiscal Year | Responses to Clinical Holds Received | Actions Within Goal | | | Actions Overdue | | | % Completed Within Goal[1] | *PDUFA Goal* |
|---|---|---|---|---|---|---|---|---|---|
| | | Completed | Pending | Total | Completed | Pending | Total | | |
| FY 1998 | 22 | 18 | 0 | 18 | 4 | 0 | 4 | 82% | *75%* |
| FY 1999 | 77 | 73 | 0 | 73 | 4 | 0 | 4 | 95% | *90%* |
| FY 2000 | 89 | 87 | 0 | 87 | 2 | 0 | 2 | 98% | *90%* |
| FY 2001 | 125 | 115 | 0 | 115 | 10 | 0 | 10 | 92% | *90%* |
| FY 2002 | 122 | 112 | 7 | 119 | 3 | 0 | 3 | 97% | *90%* |

[1] - of those that have reached the goal date

# Number of Cycles to Approval

- From CY 1995-2001, OTRR approved 41% of the original BLAs submitted within 1 cycle
- 19% took 3 or more cycles
- Numbers are comparable to NMEs approved during this same time period

# Number of Approvals Within 12 Months

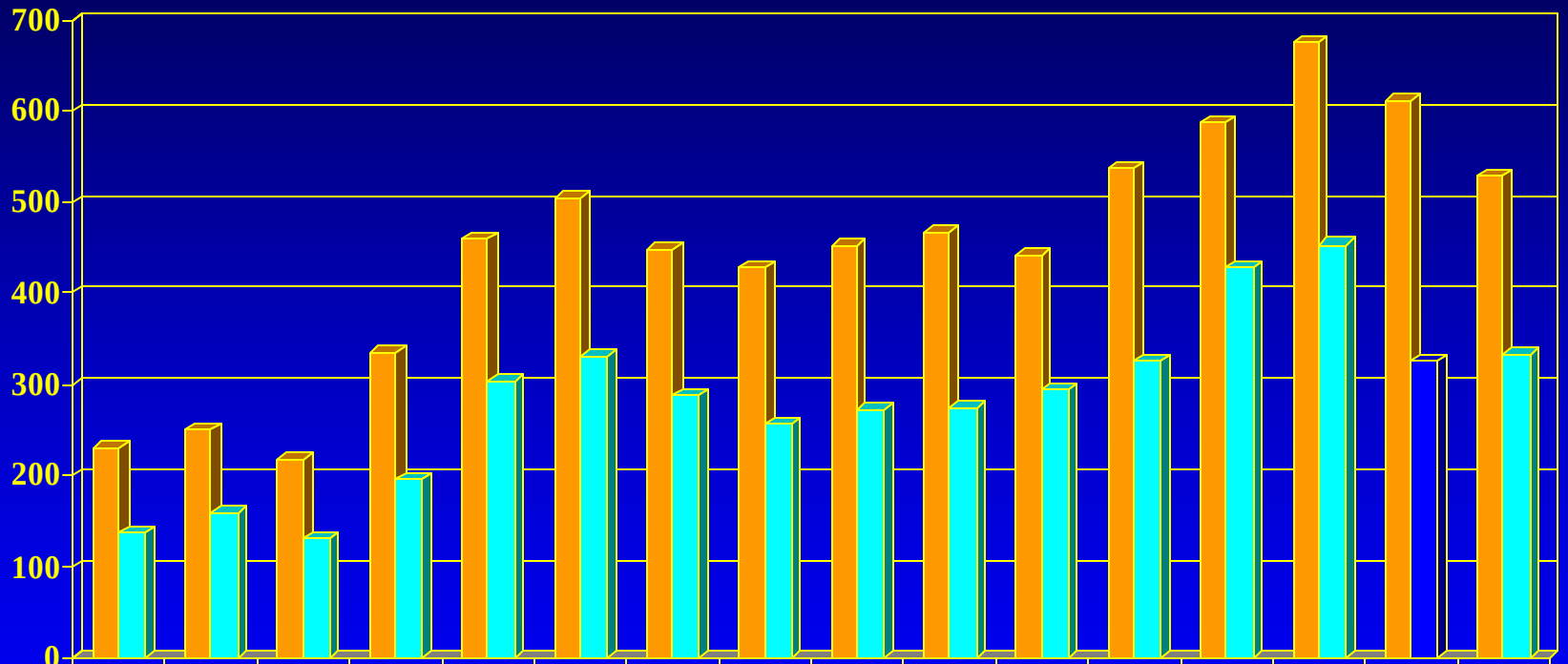
- CY 1996-2000, 14 of 22 BLAs submitted to OTRR approved within 12 months (64%)
- 13 were priority review; 10 within 12 months
- 9 were standard review; 4 approved within 12 months

# OTRR Meeting Goal Performance Under PDUFA II

- **Response to Meeting Requests: 99% within goal**
- **Meetings Held: 99% within goal**
- **Meeting Minutes: 99% within goal**
- **Non-PDUFA Products: 97%, 97% and 94%, respectively**

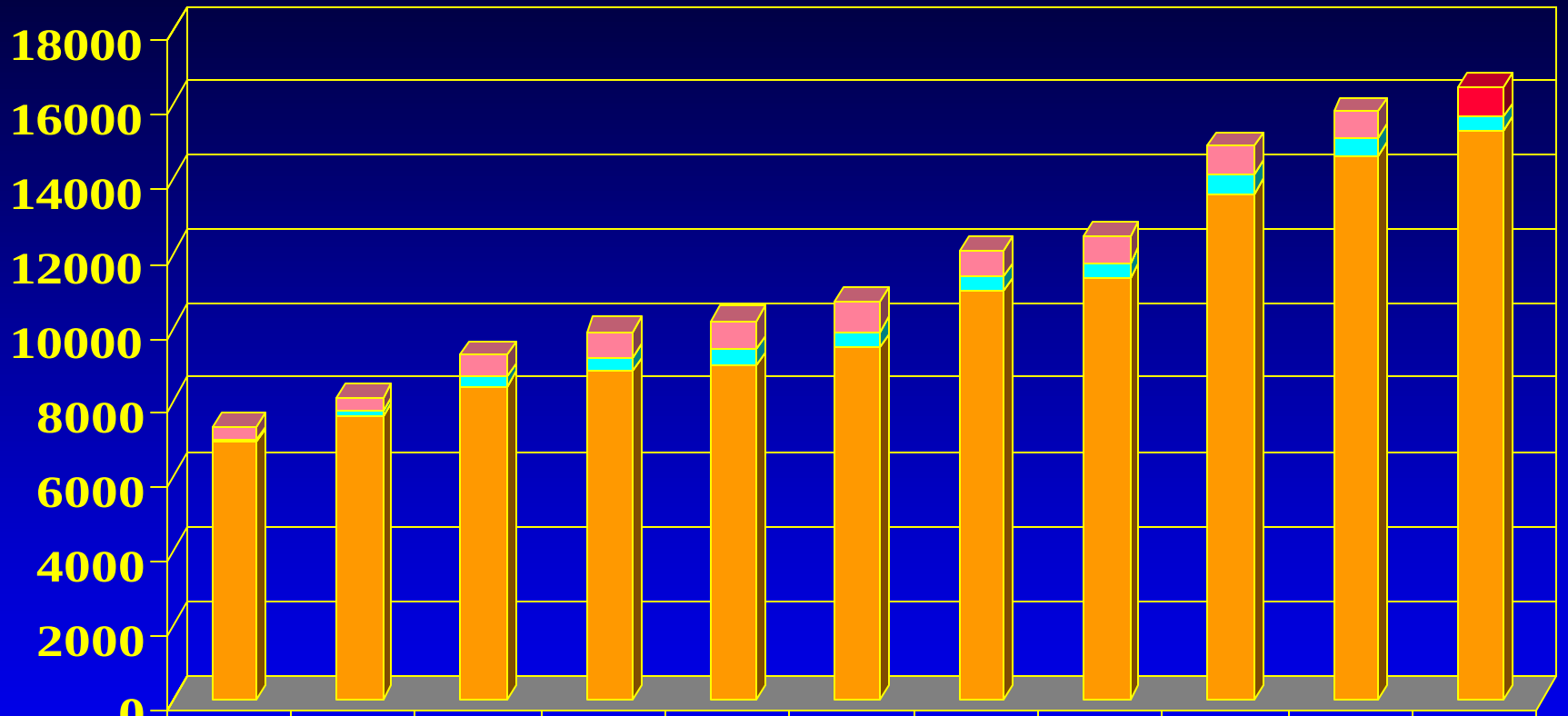
**Source: FY 2001 Report to Congress**

# CBER INDs/IDEs
## Received FY 1987 - FY 2002




| | FY87 | FY88 | FY89 | FY90 | FY91 | FY92 | FY93 | FY94 | FY95 | FY96 | FY97 | FY98 | FY99 | FY00 | FY01 | FY02 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total INDs/IDEs Received | 231 | 250 | 217 | 335 | 459 | 505 | 449 | 428 | 452 | 467 | 442 | 538 | 587 | 674 | 611 | 528 |
| Biotech INDs/IDEs | 138 | 159 | 131 | 196 | 304 | 331 | 288 | 257 | 273 | 275 | 295 | 327 | 427 | 453 | 326 | 333 |

# CBER IND/IDE/MF Amendments
## Received FY92-FY02




| | FY92 | FY93 | FY94 | FY95 | FY96 | FY97 | FY98 | FY99 | FY00 | FY01 | FY02 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MFs | 382 | 365 | 611 | 713 | 780 | 812 | 678 | 698 | 779 | 697 | 837 |
| IDEs | 54 | 130 | 210 | 375 | 457 | 431 | 397 | 386 | 516 | 480 | 355 |
| INDs | 6914 | 7628 | 8453 | 8827 | 8966 | 9479 | 10988 | 11371 | 13620 | 14628 | 15299 |

# CBER Biologics License Applications and Supplements Received

| | FY 2000 | FY 2001 | FY 2002 |
|---|---|---|---|
| **BLAs** | **25** | **18** | **18** |
| **BLSs** | **1775** | **1652** | **1786** |

Numbers exclude Mergers/Corporate Entity Changes

# PERFORMANCE GOALS
# PDUFA II vs. PDUFA III

- **Original NDA/BLA Submissions: No Change**
- **Original NDA/BLA Resubmissions: No Change**
- **Original Efficacy Supplements: No Change**
- **Resubmitted Efficacy Supplements: Modified**
- **Original Manufacturing Supplements: No Change**
- **New Molecular Entity (NME): No Change**
- **Clinical Holds: No Change**
- **Major Dispute Resolution: No Change**
- **Special Protocol Question : No Change**

**Meeting Management: Technical Change**

C B
E R

# PDUFA III – NEW PROGRAMS

- **Continuous Marketing Application (CMA)**
- **Independent Consultants for Biotechnology Clinical trial Protocols**
- **Pre and Peri-NDA/BLA Risk Management Plan Activities**
- **First Cycle Review Performance Proposal**
- **Improving FDA Performance Management**
- **Electronic Applications and Submissions**

# Electronic Submissions Goals

- Assist the reviewer community in meeting PDUFA review goals
- Provide reviewers with intuitive, standard presentations and tools to review electronic submissions effectively
- Provide the ability to manage all CBER submission types, starting with INDs, BLAs, and Promotional Labeling (current) with future functionality for 510(k)s and PMAs

# Electronic Submissions Goals

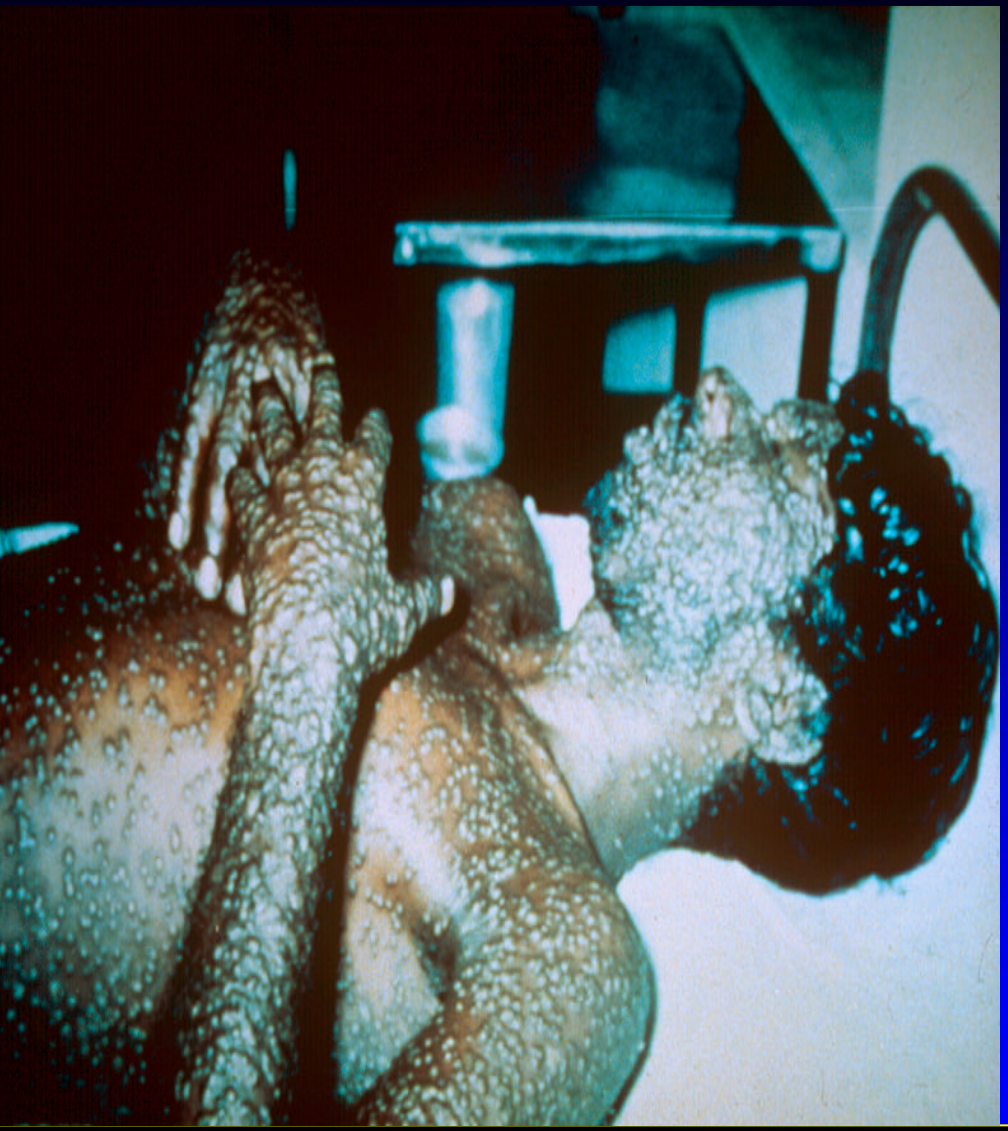
- Establish electronic submissions standards and guidance for Industry
- Enable CBER to meet PDUFA and FDAMA electronic submissions mandates and timelines
- Decrease administrative processing time and costs of the submission process
- Enhance processes through electronic routing and secure transmission of information

# Submission & Review Tools

- Electronic Document Room (EDR)
  - Provides the core system for CBER e-subs
- Electronic Secure Messaging (ESM)
  - Provides a secure communications channel between CBER and Industry
- Electronic Signature
  - Digital signatures compliant with 21 CFR Part 11
- E-Routing
  - Provides fully electronic workflow for routing

# Status

- CBER is the first Center to accept fully electronic regulatory documents with digital signatures and automated submission and processing via ESM
- The EDR, ESM, and e-Routing are a complete, robust set of review tools to meet reviewer needs, developed in conjunction with the reviewer community
- CBER's electronic submission infrastructure and applications may form the core of an overall FDA electronic submission toolset
- The CBER Electronic Submissions program is robust and has made great strides since its inception in 1996




# COUNTER- BIOTERRORISM

# Countering Bioterrorism
# CBER

- Facilitate the availability of necessary medical products
- Scientific infrastructure to ensure availability of approved medical products
- Ensure availability of specialized equipment and facilities for containment
- Establish and disseminate the necessary guidance/standards

# Key Actions
# CBER

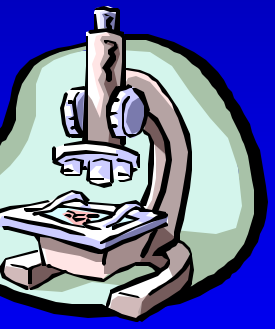
- Expedite development and licensure of new vaccines for anthrax, smallpox, and associated VIG
- Develop new approaches to approve medical products for countering bioterrorism
- Continue activities related to stockpile and product shortages
- Participate in numerous collaborative activities with other government agencies

# Shepherding Safe and Effective Products

**Regulatory Research**

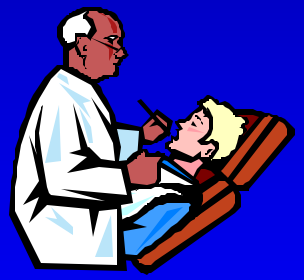
**FDA**

**Bench** **Bedside** **Marketplace**



**Translational Research**

**NIH**
**Academia**
**Industry**



**Pharmaceutical Research**

**Industry**

**BASIC** **APPLIED** **SAFETY & QUALITY**

# CBER Research Priorities FY 2003

## Biotechnology

- Genomics/Proteomics
- Stem Cell Products/Tissue Engineering
- Transgenic Plants and Animals